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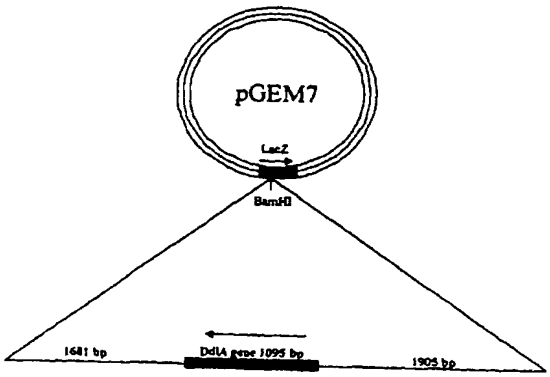
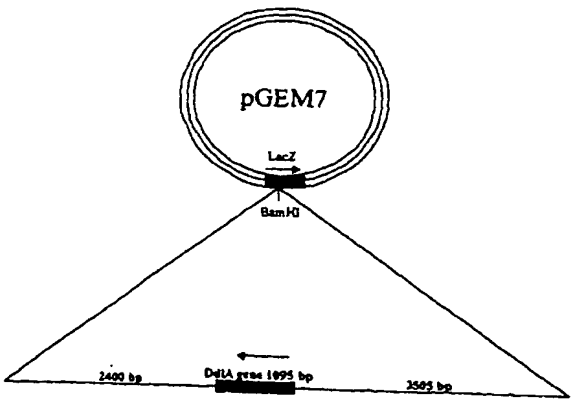
[Continued on next page]

(54) Title: USE OF QUINAZOLINE DERIVATIVES OR OTHER COMPOUNDS FOR INHIBITING DIHYDROFOLATE REDUXTASE; SCREENING ASSAY FOR THE IDENTIFICATION OF NOVEL THERAPEUTICS AND THEIR CELLULAR TARGETS





(57) Abstract: A novel screening assay for identifying therapeutic agents and their cellular targets is described. The assay is useful in developing new antibacterial, antifungal, antiparasitic and anti cancer therapeutics. New inhibitors of dihydrofolate reductase (DHFR) have been identified using the assay of the present invention. Methods of treating diseases that benefit from an inhibition of DHFR are also described.

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(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]A2004/000151

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/517 A61K31/53 A61K31/17 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, SCISEARCH, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ZOLLI-JURAN M ET AL: "HIGH THROUGPUT SCREENING IDENTIFIES NOVEL INHIBITORS OF ESCHERICHIA COLI DIHYDROFOLATE REDUCTASE THAT ARE COMPETITIVE WITH DIHYDROFOLATE" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 13, no. 15, 2003, pages 2493-2496, XP009020750 ISSN: 0960-894X table 1 page 2496, column 1, paragraph 2 - column 2, paragraph 1 ----- -/--	1,2,6-8, 13-16, 20-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 2004	-8. 10. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

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INTERNATIONAL SEARCH REPORT

International Application No
[redacted]CA2004/000151

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/50370 A (KUTSCHER BERNHARD ; WEINBERGER HEINZ (DE); SUGEN INC (US); TANG PENG C) 12 November 1998 (1998-11-12) claims 1,10,13,14,33 claims 16,32; examples a4,a5,a7,a9,a18 page 32, line 21 - page 33, line 4 page 52, line 4 - page 53, line 16	1,2,6-8, 13-16, 20-27
X	GOKHALE, VIJAY M. ET AL: "Selectivity analysis of 5-(arylthio)-2,4-diaminoquinazolines as inhibitors of Candida albicans dihydrofolate reductase by molecular dynamics simulations" JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN , 14(5), 495-506 CODEN: JCADEQ; ISSN: 0920-654X, 2000, XP008031600 examples 1,7-9; table 1 page 495, column 1, paragraph 1 - column 2, paragraph 2	1,2,6-8, 13-16, 20-27
L	ASHTON, WALLACE T. ET AL: "Synthesis of 5-substituted quinazolines as potential antimalarial agents" JOURNAL OF MEDICINAL CHEMISTRY , 16(11), 1233-7 CODEN: JMCMAR; ISSN: 0022-2623, 1973, XP001149467 examples 6b,7; table 1 page 1233, column 1, paragraph 1 - paragraph 2	1,2,6-8, 13-16, 20-27
L	NEIL V HARRIS: "ANTIFOLATE AND ANTIBACTERIAL ACTIVITIES OF 5-SUBSTITUTED 2,4-DIAMINOQUINAZOLINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 1, no. 33, 1990, pages 434-444, XP002074317 ISSN: 0022-2623 examples 60,64; table IV	
A	HANSCH C ET AL: "QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS OF ANTIMALARIAL AND DIHYDROFOLATE REDUCTASE INHIBITION BY QUINAZOLINES AND 5-SUBSTITUTED BENZYL-2,4-DIAMINOPYRIMIDINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 20, no. 1, 1977, pages 96-102, XP002931294 ISSN: 0022-2623 example 33; table 1 example 14; table IV page 96, column 1, paragraph 1	

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Form PCT/ISA/210 (continuation of second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/18980 A (FMC CORP) 1 September 1994 (1994-09-01)	
A	ROSOWSKY A ET AL: "2,4-DIAMINO-5-SUBSTITUTED-QUINAZOLINES AS INHIBITORS OF A HUMAN DIHYDROFOLATE REDUCTASE WITH A SITE-DIRECTED MUTATION AT POSITION 22 AND OF THE DIHYDROFOLATE REDUCTASES FROM PNEUMOCYSTIS CARINII AND TOXOPLASMA GONDII" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 5, 1995, pages 745-752, XP000197454 ISSN: 0022-2623	
A	HYNES JB ET AL: "Quinazolines as inhibitors of dihydrofolate reductase. 4. Classical analogues of folic and isofolic acids" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 20, no. 4, 1977, pages 588-591, XP002155519 ISSN: 0022-2623	
L	J. MED. CHEM., vol. 36, 1993, pages 733-746, XP001149469 page 737; examples 4,5; table I page 738, column 1 - column 2	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/000151

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 36-38,40
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1,2,6-7,13,15,16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 36-38,40
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

6, 13-16, 20-27 (all partially), 1, 2 , 7, 8

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1,2,6-7,13,15,16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 36-38,40

Claims 36-38,40 encompass a genus of compounds defined only by their function (therapeutic agent identified using the screening method of claims 30-35) wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, no search has been performed for claims 36-38,40 (Articles 5,6 PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 6,13-16,20-27 (partially) 1,2,7,8

Use of quinazoline derivatives falling under formula I for treating conditions that benefit form an inhibition of dihydrofolate reductase (DHFR) and use in vitro for inhibiting DHFR.

---

2. claims: 6,13-16,20-27 (partially) 3,4,9,10

Use of quinazolidine derivatives falling under formula II for treating conditions that benefit form an inhibition of dihydrofolate reductase (DHFR) and use in vitro for inhibiting DHFR.

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3. claims: 5,6,11-16,20-27 (partially)

Use of the compound 8 of table 1 for treating conditions that benefit form an inhibition of dihydrofolate reductase (DHFR) and use in vitro for inhibiting DHFR.

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4. claims: 5,6,11-16,20-27 (partially), 17-19,28-29

Use of compounds 9 and 11 of table 1 for treating conditions that benefit from an inhibition of dihydrofolate reductase (DHFR) and use in vitro for inhibiting DHFR.

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5. claims: 5,6,11-16,20-27 (partially)

Use of compound 10 of table 1 for treating conditions that benefit from an inhibition of dihydrofolate reductase (DHFR) and use in vitro for inhibiting DHFR.

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6. claims: 30-35,39

Method for identifying a candidate therapeutic agent by contacting the test agents with two target cells and comparing the growth of the two target cells as described in claim 30.

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7. claims: 41,42

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method of conducting a drug discovery business providing an assay system for identifying potential therapeutic agents, then conducting therapeutic profiling of agents so identified, and formulating a pharmaceutical preparation including them.

INTERNATIONAL SEARCH REPORT

[redacted]formation on patent family members

International Application No
[redacted]/CA2004/000151

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		WO	9418980 A1	01-09-1994
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